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(54) Title: CRYSTALLINE FORMS OF LANSOPRAZOLE

(57) Abstract: According to the invention, a phenomenon of polymorphism of 2-{[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl}-sulfinylo-1H-benzimidazole (lansoprazole) is disclosed. The crystalline forms I and II of lansoprazole were obtained and identified and a method of preparation of lansoprazole in the pharmaceutically advantageous crystalline form I was developed. The form I finds application as an active ingredient of pharmaceutical compositions.

Crystalline forms of lansoprazole

The object of the invention are crystalline forms of lansoprazole and a method of preparation of lansoprazole in the pharmaceutically advantageous crystalline form.

Lansoprazole - 2-{[3-methyl-4-(2,2,2,-trifluoro-ethoxy)-2-pyridinyl]methyl}-sulfinyl-1H-benzimidazole, is known from pharmaceutical practice as a drug inhibiting secretion of gastric juice, used in the treatment of gastric and duodenal ulcers.

Lansoprazole - as a chemical compound - is known from European Patent EP 0174726.

In European Patent EP 0302720 a method of preparation of lansoprazole consisting in reaction of oxydation of 2-{[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl} tio-1H-benzimidazole - with the use of hydrogen peroxide in the presence of catalytic amounts of vanadium pentoxide - is disclosed. The resulting crude lansoprazole is purified by crystallization from aqueous ethanol (90%), to yield the product containing more than 99% of the main compound.

Another method of preparation of lansoprazole, described in European Patent EP 0174726 and in a

publication [Chem.Pharm.Bull. 38(10), 2853(1990)] consists in the use of m-chloroperbenzoic acid as an oxydation agent. The crude product is purified on a column (silica gel, eluent: ethyl acetate), and then subjected to crystallization from a mixture of solvents: acetone-ethyl ether-hexane.

In the above-mentioned patent specifications as well as in chemical literature no reports concerning polymorphic forms of lansoprazole have been found.

A great number of biologically active compounds crystallizes forming various crystallographic structures. Such a phenomenon is called polymorphism. In case of pharmaceuticals polymorphism may be regarded as a disadvantageous feature. Individual polymorphic forms exhibit different chemical stability and reactivity in relation to auxiliary substances and fillers in the finished drug. In some cases considerable differences in their solubility are also observed. Possibility of conversion of one crystalline form into another depending on conditions of preparation, storage or use of a pharmaceutical formulation, that contains one of polymorphic forms of a compound in question as an active ingredient, involves problems as regards prediction of stability and bioavailability of that active ingredient, which guarantees therapeutic effect, and causes that in therapy only one of the polymorphic forms of the substance in question is used.

During our experimental work we haave found that

carrying out the oxydation reaction of 2-{[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl}tio-1H-benzimidazole as a step of the method described in European Patents Nos. EP 0302720 and EP 0174726, and purifying the crude product by crystallization, depending on a solvent used for crystallization and on a method of carrying out crystallization, lansoprazole of high degree of chromatographic purity (more than 99%) is produced, but in various crystallographic forms, defined hereafter as the form I or form II, or as a mixture of the forms I and II, possibly as a solvate of one of the forms with a molecule of a solvent.

Infrared spectra (IR, shown in Fig.1) of the two polymorphic forms of lansoprazole made by technique of pressed tablets with potassium bromide (Spectrometer FTIR, Perkin Elmer 1725X) are distinctly different, especially in the range of vibrations that stretch N-H and C-H.

Powder diffraction patterns (Powder diffraction instrument DRON-4) of both polymorphic forms also substantially differ from each other.

Analysis of IR spectra of one of the forms called the crystalline form I indicated that it corresponds to a crystalline form of lansoprazole present in pharmaceutical formulations already approved for therapy, characterized by presence of the following bands in IR spectrum: 3234 (broad band), 2984, 2931, 1581, 1478, 1457, 1402, 1268, 1173, 1119, 1039, 972,

858, 814 and 750 cm-1.

The crystalline form I is characterized by X-ray powder diffraction pattern shown on Fig.2 and in the corresponding Table 1 as an interdependence of intensities of relative diffraction lines CuKα at the wavelength λ=1.541 A, diffraction values θ and interplanar distances d.

Table 1.

2θ (deg)	d (A)	Relative intensity
5.56	15.894	100
6.85	12.942	50
7.39	11.966	1
11.24	7.875	21
12.60	7.026	7
13.14	6.740	2
13.45	6.581	1
14.05	6.305	17
14.81	5.981	1
16.73	5.299	46
17.37	5.104	46
18.47	4.804	17
19.18	4.628	3
22.16	4.012	31
22.74	3.910	17
23.31	3.815	11
24.04	3.702	1
24.79	3.591	21
25.63	3.475	21

26.61	3.350	2
27.61	3.231	27
28.51	3.131	7
29.18	3.060	2
30.10	2.968	9
30.52	2.928	4
31.09	2.877	11
31.53	2.838	1
32.40	2.763	1
32.89	2.723	6
33.38	2.684	4
33.81	2.651	1
34.48	2.601	2
34.93	2.568	4
35.97	2.497	2
36.64	2.453	1
37.45	2.402	2
37.91	2.373	2
38.50	2.338	1
39.33	2.291	4

In the case of the form I measurements by differential scanning calorimetry (DSC) exhibited a maximum at 183.57°C.

In IR spectra (Fig. 1b) of the polymorphic form II presence of the following bands is found: a broad band with multiple maxima in the range 3062-2608, 1580, 1476, 1459, 1436, 1268, 1173, 1115, 1019, 974, 858, 812, 744 cm^{-1}.

The crystalline form II is characterized by X-ray

powder diffraction pattern shown on Fig.3 and in the corresponding Table 2 as an interdependence of intensities of relative diffraction lines CuKα, diffraction values θ and interplanar distances d.

Table 2.

2θ (deg)	d (A)	Relative intensity
5.16	17.134	95
5.54	15.956	46
6.77	13.050	100
7.40	11.951	1
10.03	8.817	1
10.44	8.469	13
11.17	7.921	11
12.52	7.071	3
13.02	6.798	1
13.22	6.699	1
14.02	6.317	3
14.71	6.022	1
15.76	5.624	9
16.73	5.298	8
17.81	4.981	35
18.50	4.796	9
19.95	4.451	1
20.20	4.396	1
21.13	4.205	10
21.66	4.103	1
22.09	4.023	3
22.67	3.922	8

23.32	3.815	2
23.99	3.709	1
24.74	3.599	5
25.38	3.509	7
26.55	3.357	1
27.68	3.222	18
28.39	3.143	7
29.91	2.987	1
30.49	2.931	1
31.03	2.882	2
32.05	2.793	3
32.91	2.722	2
33.74	2.657	1
34.46	2.602	1
35.00	2.563	1

It has been found that the resulting crystalline form of lansoprazole depends on a method used for purification of crude lansoprazole produced by oxydation of 2-{[3-methyl-4-(2,2,2-trifluoroethoxy-2-pyridinyl]methyl}tio-1H-benzimidazole.

When purifying crude lansoprazole by crystallization from aqueous ethanol (up to 10% water content), the crystalline form II is obtained, characterized by X-ray powder diffraction pattern according to Table 2. Measurements by differential scanning calorimetry (DSC) exhibited a presence of maximum at 182.38°C.

The crystalline form II is stable at temperatures

below 0°C. IR spectrum of the form II does not change after one-year storage of samples at temperature -5°C. However, after some period of sample storage at higher temperatures, bands in IR spectra, that are characteristic for the form I of lansoprazole, are observed.

The crystalline form I of lansoprazole is characterized by high stability. Spectral analysis performed after one-year storage of the substance at room and elevated temperatures exhibited identical spectra IR and powder diffraction patterns. Thus, the crystalline form I is the form pharmaceutically advantageous, stable under conditions of preparation and storage of pharmaceutical formulations containing lansoprazole as an active ingredient.

A further aspect of the invention is a method of preparation of lansoprazole in the pharmaceutically advantageous crystalline form.

The method of preparation of lansoprazole in the pharmaceutically advantageous crystalline form I consists in that a crude lansoprazole is subjected to crystallization from aqueous ethanol containing up to 10% water, at temperature from 20°C to 60°C, preferably 55-60°C, and then the resulting lansoprazole (of chromatographic purity of at least 99%) is crystallized from acetone and isolated by a known method.

The method according to the invention makes it possible to obtain lansoprazole in the stable

crystallographic form I, characterized by X-ray powder diffraction pattern consistent with the appended Table 1.

The method according to the invention may be applied especially for purification of lansoprazole produced in oxydation reaction of 2-{[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl}tio-1H-benzimidazole, but it is not limited to that method of the substance synthesis.

Lansoprazole exhibiting the desired spectral characteristics can be produced by crystallization from acetone of the substance occuring in other, less stable crystalline form or by crystallization of mixture of various crystalline forms of lansoprazole.

The invention is illustrated by the following examples of embodiments, that are not intended to limit the scope of the invention.

Example 1.

A crude lansoprazole (35 g), prepared in oxydation reaction of 2-{[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl}tio-1H-benzimidazole was added to 300 ml 90% ethanol heated to temperature 55°C. After filtering and cooling the resulting mixture to temp. below 0°C, the precipitate was filtered off and washed with 50% ethanol (50 ml). The moist precipitate was dried at a temperature not exceeding 50°C, to yield the polymorphic form II with a small amount of the form I. A yield amounted to more

than 90%.

IR (KBr) cm-1: 3062-2608 (a broad band with multiple maxima), 1580, 1476, 1459, 1436, 1268, 1173, 1115, 1019, 974, 858, 812, 744.

DSC-max 182.38°C. H_2O content: 0.08%.

Example 2.

Lansoprazole prepared as in Example 1 (100 g) was dissolved at boiling temperature in 1500 ml of acetone. After filtration the solution was cooled to room temperature, and then slowly cooled for 3 hours to attain temperature 0°C. After filtering off, the resulting precipitate was dried for 2 hours at temperature below 50°C, to yield lansoprazole in the crystallographic form I. Yield >95%.

IR (KBr), cm-1: 3234 (broad band), 2984, 2931, 1581, 1478, 1457, 1402, 1268, 1173, 1119, 1039, 972, 858, 814 and 750.

DSC-max 183.57°C. H_2O content: 0.08%.

Claims

1. Crystalline form I of lansoprazole characterized by the following X-ray powder diffraction pattern showing interdependence of intensities of relative diffraction lines CuKα, diffraction values θ and interplanar distances d:

2θ (deg)	d (A)	Relative intensity
5.56	15.894	100
6.85	12.942	50
7.39	11.966	1
11.24	7.875	21
12.60	7.026	7
13.14	6.740	2
13.45	6.581	1
14.05	6.305	17
14.81	5.981	1
16.73	5.299	46
17.37	5.104	46
18.47	4.804	17
19.18	4.628	3
22.16	4.012	31
22.74	3.910	17
23.31	3.815	11
24.04	3.702	1
24.79	3.591	21

25.63	3.475	21
26.61	3.350	2
27.61	3.231	27
28.51	3.131	7
29.18	3.060	2
30.10	2.968	9
30.52	2.928	4
31.09	2.877	11
31.53	2.838	1
32.40	2.763	1
32.89	2.723	6
33.38	2.684	4
33.81	2.651	1
34.48	2.601	2
34.93	2.568	4
35.97	2.497	2
36.64	2.453	1
37.45	2.402	2
37.91	2.373	2
38.50	2.338	1
39.33	2.291	4

2. Crystalline form I of lansoprazole according to Claim 1, characterized by IR spectrum shown in Fig.1a.

3. Crystalline form II of lansoprazole characterized by the following X-ray powder diffraction pattern showing interdependence of intensities of relative diffraction lines CuKα, diffraction values θ and interplanar distances d:

2θ (deg)	d (A)	Relative intensity
5.16	17.134	95
5.54	15.956	46
6.77	13.050	100
7.40	11.951	1
10.03	8.817	1
10.44	8.469	13
11.17	7.921	11
12.52	7.071	3
13.02	6.798	1
13.22	6.699	1
14.02	6.317	3
14.71	6.022	1
15.76	5.624	9
16.73	5.298	8
17.81	4.981	35
18.50	4.796	9
19.95	4.451	1
20.20	4.396	1
21.13	4.205	10
21.66	4.103	1
22.09	4.023	3
22.67	3.922	8
23.32	3.815	2
23.99	3.709	1
24.74	3.599	5
25.38	3.509	7
26.55	3.357	1

27.68	3.222	18
28.39	3.143	7
29.91	2.987	1
30.49	2.931	1
31.03	2.882	2
32.05	2.793	3
32.91	2.722	2
33.74	2.657	1
34.46	2.602	1
35.00	2.563	1

4. Crystalline form II of lansoprazole according to Claim 3, characterized by IR spectrum shown on Fig.1b.

5. Method of preparation of lansoprazole in the pharmaceutically advantageous crystalline form I, wherein the crude lansoprazole is subjected to crystallization from ethanol containing up to 10% water, at a temperature from 20°C to 60°C, preferably 55-60°C, and then the resulting lansoprazole of chromatographic purity of at least 99% is crystallized from acetone and isolated by a known method.

6. Method of preparation of lansoprazole in the pharmaceutically advantageous crystalline form I, wherein the lansoprazole resulting from oxydation reaction of 2-{[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methyl}tio-1H-benzimidazole is subjected to crystallization.

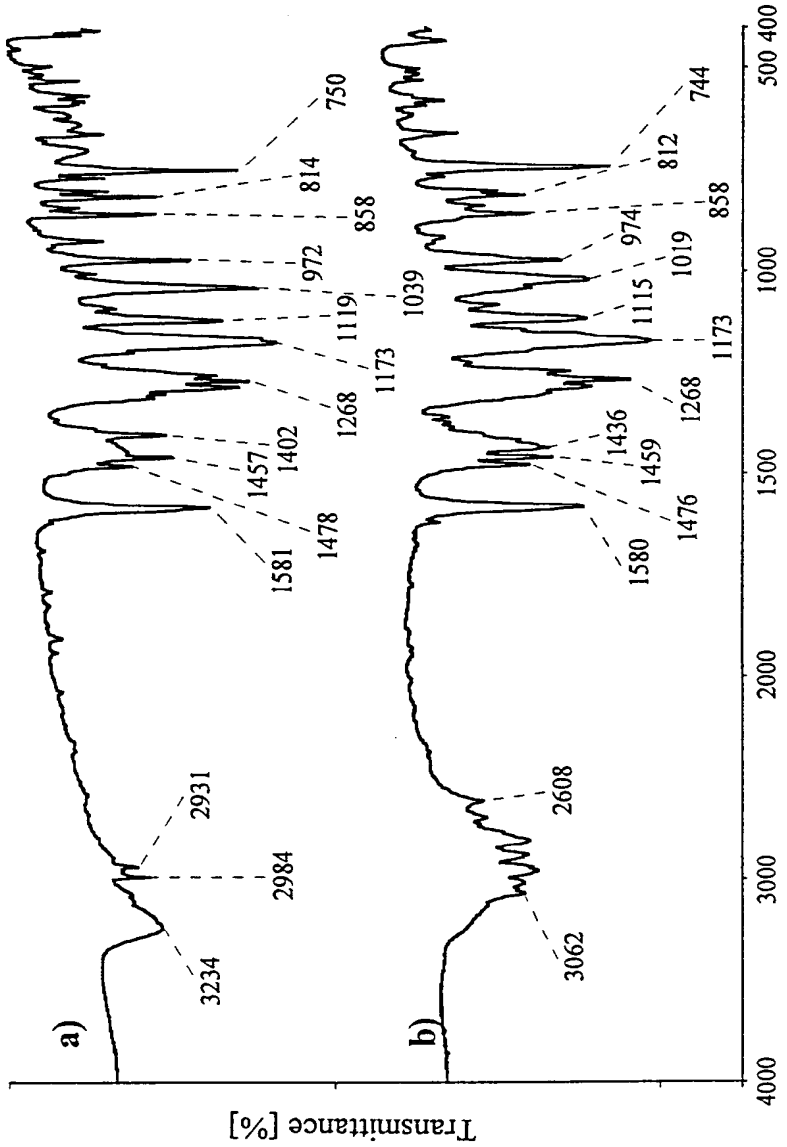

Fig.1. IR spectra of the polymorphic forms of lansoprazole
a) form I
b) form II

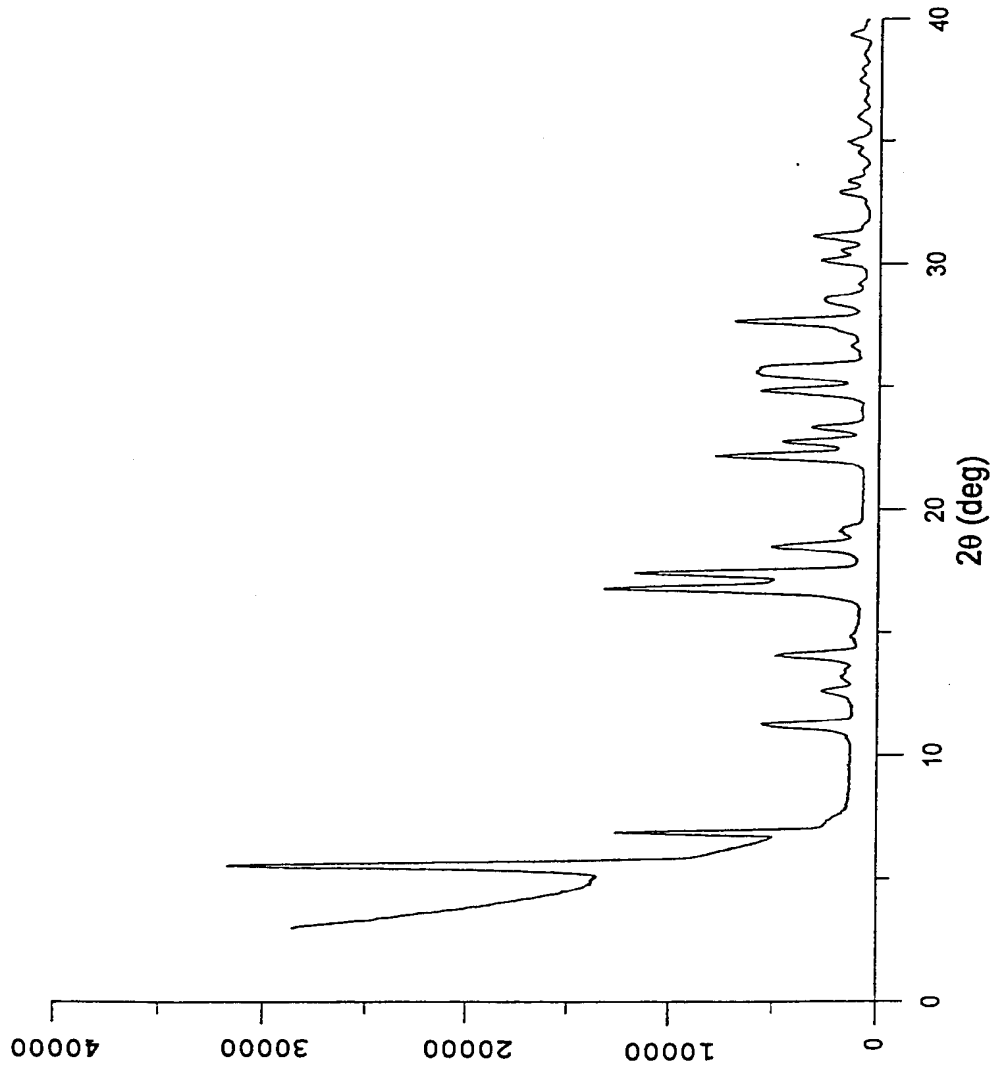

Fig.2. X-Ray powder diffraction pattern of the crystalline form I of lansoprazole

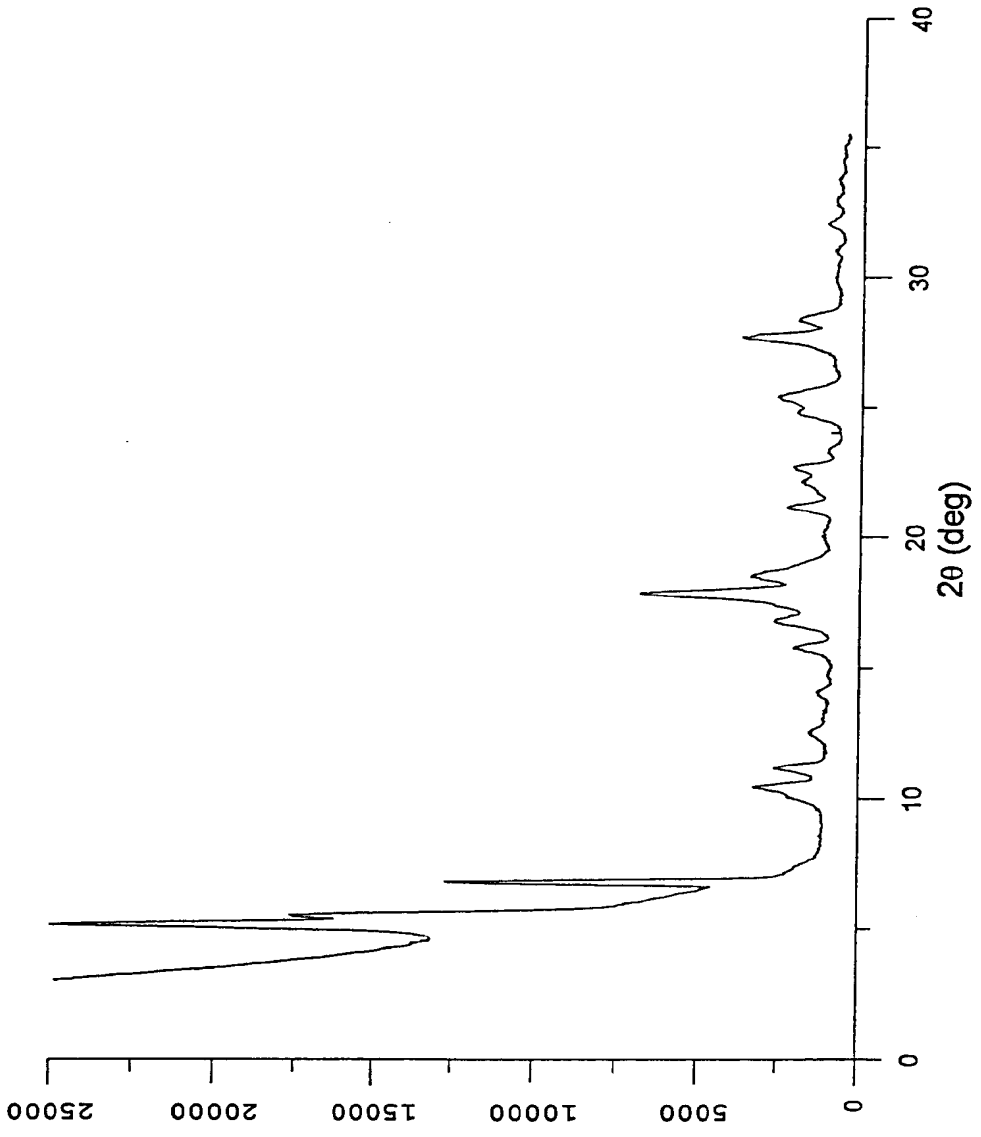

Fig.3. X-Ray powder diffraction pattern of the crystalline form II of lansoprazole

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/PL 00/00042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D235/28 //A61K31/4184,A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 302 720 A (TAKEDA CHEMICAL INDUSTRIES, LTD.) 8 February 1989 (1989-02-08) cited in the application the whole document, particularly examples 1-4 ---	1-6
X	KUBO K ET AL: "Synthesis of 2-''(4-fluoroalkoxy-2-pyridyl)methyl! sulfinyl!-1H-benzimidazoles as antiulcer agents" CHEMICAL & PHARMACEUTICAL BULLETIN, vol. 38, no. 10, October 1990 (1990-10), pages 2853-2858, XP002150630 cited in the application the whole document, particularly page 2856, table IV, compound 6f --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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20 October 2000	07/11/2000

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	VRECER F ET AL: "Study of influence of temperature and grinding on the crystalline state of lansoprazole" FARMACEVTSKI VESTNIK, vol. 48, 1997, pages 242-243, XP000946952 Ljubjana the whole document	1-6
X	SITAR CURIN A ET AL: "Study of crystal modifications of lansoprazole using FT-IR spectroscopy, solid-state NMR spectroscopy and FT-Raman spectroscopy" FARMACEVTSKI VESTNIK, vol. 48, 1997, pages 290-291, XP000946953 Lubljana the whole document	1-6
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Information on patent family members

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